Respiratory Medicine (2009) **103**, 1098–1113

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/rmed

The use of omalizumab in the treatment of severe allergic asthma: A clinical experience update

Stephen Holgate [a,*], **Roland Buhl** [b], **Jean Bousquet** [c], **Nicola Smith** [d], **Zoya Panahloo** [d], **Pablo Jimenez** [e]

[a] *Infection, Inflammation and Repair Division, School of Medicine, University of Southampton, D level Centre Block (MP810), Southampton General Hospital, Tremona Road, Southampton SO16 6YD, UK*
[b] *Mainz University Hospital, 55131 Mainz, Germany*
[c] *Hôpital Arnaud de Villeneuve, FR-34000 Montpellier, France*
[d] *Novartis Horsham Research Centre, Horsham, RH12 5AB, UK*
[e] *Novartis Pharmaceuticals Corporation, East Hanover, NJ 07936-1080, USA*

Received 20 October 2008; accepted 12 March 2009
Available online 10 April 2009

KEYWORDS
Omalizumab;
Immunoglobulin E (IgE);
Allergic asthma;
Respiratory

Summary
Severe persistent asthma causes a substantial morbidity and mortality burden and is frequently inadequately controlled despite intensive guideline-based therapy. Targeting allergic inflammatory processes that underlie the pathogenesis of severe persistent asthma improves asthma control in a significant proportion of patients. Omalizumab, a humanized monoclonal anti-immunoglobulin E (IgE) antibody, has been developed to target IgE, which is central to triggering and maintaining allergic airway inflammation. In a comprehensive program of clinical trials, omalizumab has been shown to reduce asthma exacerbation and emergency visit rates, and to improve quality of life in patients with severe persistent allergic asthma. It is difficult to predict which patients would most benefit from omalizumab treatment; accurate selection and dosing of patients are essential to achieve benefit. Patients need to have convincing IgE-mediated asthma and be dosed according to pre-treatment serum total IgE level and body weight, using a specified dosing table. Based on clinical trial data analysis, it is recommended that treatment response is evaluated by the physician after 16 weeks of therapy. Treatment should only be continued in responders, i.e. those judged by the physician to have achieved a marked improvement or complete asthma control. Omalizumab is generally well tolerated. Anaphylactic-like reactions are rare (0.1% of patients) and less common than encountered with other biologics.
© 2009 Published by Elsevier Ltd.

* Corresponding author. Tel.: +44 (0) 23 8079 6960; fax: +44 (0) 23 8070 1771.
E-mail address: s.holgate@soton.ac.uk (S. Holgate).

0954-6111/$ - see front matter © 2009 Published by Elsevier Ltd.
doi:10.1016/j.rmed.2009.03.008

Scope of review

Several reviews have been published recently on the efficacy and safety of omalizumab in the treatment of adolescents and adults with moderate-to-severe allergic (IgE-mediated) asthma.[1–4] Additional reviews have discussed the anti-inflammatory effects of omalizumab[5] as well as the cost-effectiveness of omalizumab in the treatment of severe allergic asthma.[6] This publication is intended to provide a review of the literature pertaining to potential issues around the safety of omalizumab, highlighted in the prescribing information, as well as data in the public domain.

Methodology

In selecting studies to include in this review, a literature search for relevant material was conducted using the MedLine database (1970–2008). Publications which addressed or provided insight into the areas for discussion were hand-picked, including some which were funded by the manufacturer of omalizumab to address questions from regulatory authorities during the licensing process.

Introduction

Asthma is a serious health problem that affects people of all ages throughout the world.[7] The Global Initiative for Asthma (GINA) treatment guidelines emphasize that clinical management should be based on clinical control rather than asthma severity, which can change over time. Asthma control is defined in the latest update of the GINA guidelines (2007) as no daytime symptoms, no limitations of daily activities, no nocturnal symptoms, no need for reliever treatment, normal or near-normal lung function and no exacerbations.[7] GINA guidelines recommend that controller medications, i.e. daily treatment to keep asthma under control, be tailored for each patient in a stepwise approach (Fig. 1).[7] Reliever medications, i.e. those that act quickly to reverse bronchoconstriction and relieve its symptoms, are used on an as-needed basis.[7]

Although mild and moderate persistent asthma can generally be controlled with inhaled corticosteroids (ICS) and long-acting β_2-agonists (LABAs), severe persistent asthma is often inadequately controlled despite these treatments.[7,8] Furthermore, many patients with severe asthma still fail to achieve complete control despite using additional controller medications, such as leukotriene modifiers (LTRAs) or theophylline.[7] In the Gaining Optimal Asthma Control (GOAL) study, 38% of patients with the most severe asthma (defined as a daily dose of 500–1000 μg beclometasone; $n = 568$) remained inadequately controlled despite optimized treatment with ICS and a LABA (fluticasone and salmeterol).[9] In addition, 31% of patients still remained inadequately controlled despite the addition of a 4-week course of oral corticosteroids (OCS) to the treatment regimen on completion of the 1-year study. In an observational study (Epidemiological Study of Xolair Evaluating Clinical Effectiveness and Long-Term Safety in Patients with Moderate-to-Severe Asthma [EXCELS]) of the long-term clinical safety and effectiveness of the anti-immunoglobulin E (anti-IgE) antibody, omalizumab, the entry characteristics of the 5067 patients in the omalizumab cohort with moderate or severe allergic asthma were analysed using the asthma control test (ACT; a 5-item, self-administered survey designed to provide a broad assessment of asthma control over the previous 4 weeks). The scores showed that asthma was well controlled in less than half of patients (45%), while 29% were not well controlled and 26% were poorly controlled.[10]

Patients with severe asthma are at a high risk of asthma-related hospitalization and mortality.[11–14] In addition, both impairment in quality of life[15–17] and economic burden[16–18] increase with increasing asthma severity and are greatest in patients with inadequately controlled severe persistent allergic asthma.[16,19] In 1998 in a northern area of Spain, it has been estimated that severe asthma accounted for at least half of the direct and indirect costs associated with asthma.[20] There is, therefore, an urgent need for improved treatment options that will provide asthma control in these patients.

Based on findings from a European cross-sectional observational study (ENFUMOSA), approximately 50% of patients with severe asthma had a positive skin-prick test for common aeroallergens.[21] New treatment options that target allergic inflammatory processes in patients with severe persistent asthma may, therefore, provide a means to reduce the considerable individual and social burden of this inadequately controlled disease.

Allergic asthma and IgE

Asthma is an inflammatory disorder of the airways that involves several inflammatory cells and the interaction of many different mediators.[7] Allergic asthma is characterized by the presence of IgE antibodies against common allergens such as house dust mite, animal dander, pollens and moulds.[7] Initial allergen exposure results in polarization of the T lymphocyte response to a Th2 phenotype with the secretion of IL-4 and IL-13. This, combined with these cytokines from mast cells, initiates the isotype switching of IgM to the corresponding IgE directed to epitopes that may cover several loops of the allergen protein. Sensitization involves the processing of allergens by professional antigen-presenting cells and the presentation of small linear peptide epitopes to the T-cell receptor along with co-stimulation involving CD80/86 interacting with B6 on naive T cells.[22]

Subsequent exposure causes the synthesis of allergen-specific IgE, which binds to high-affinity receptors (FcεRI) on mast cells and basophils.[23] The cross-linking of two IgE molecules by the allergen triggers cell activation and degranulation, with the release of pre-formed mediators, such as histamine, heparin, and neutral proteases as well as newly formed mediators that include prostaglandin D_2, leukotriene C_4, adenosine and tumour necrosis factor (TNF)-α.[23,24] Subsequent synthesis and release of inflammatory mediators, e.g. interleukin (IL)-4, IL-5 and IL-13, promote leukocyte adhesion and, with the release of chemokines, the infiltration of circulating cells — primarily eosinophils, basophils and Th-2 cells — into the tissues, resulting in the characteristic symptoms of asthma.[23–25]

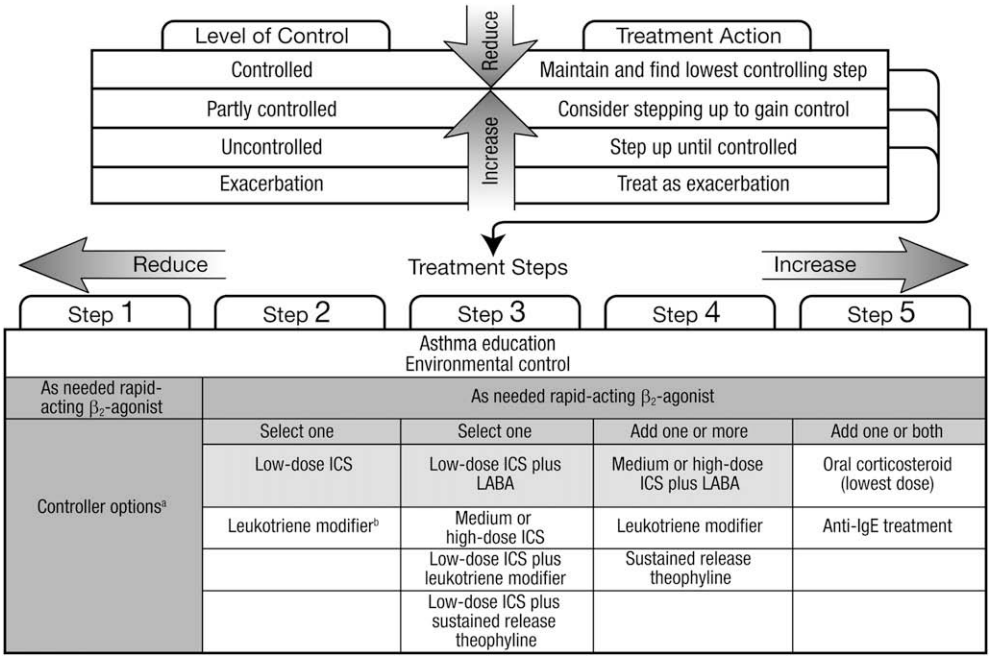


Figure 1 The GINA guidelines recommend a stepwise approach to controller medication based on level of control.[7] [a]Preferred controller options as shown in shaded boxes; [b]Receptor anatagonists or synthesis inhibitors. ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist.

Omalizumab

Mechanism of action

Omalizumab inhibits the binding of IgE to FcεRI receptors on mast cells and basophils.[5,26–28] Free IgE levels are rapidly reduced and, with less IgE available to bind, the expression of FcεRI on inflammatory cells, such as basophils, mast cells and dendritic cells, is down regulated (Fig. 2).[23,27,29] Interrupting the interaction between IgE and FcεRI inhibits mast-cell and basophil activation and the subsequent release of their inflammatory mediators. A reduction in IgE binding also leads to down-regulation of the cell surface expression of IgE and FcεRI in the airway mucosa and reduces both sputum and tissue eosinophilia.[26] By preventing the release of mast cell-derived mediators, omalizumab may reduce inflammatory cell recruitment (particularly eosinophils), tissue remodelling and functional changes in the airways.[30,31]

Because the binding site of omalizumab is buried within the FcεRI receptor, it cannot bind to IgE that is already attached to mast cells and basophils.[32,33] Consequently,

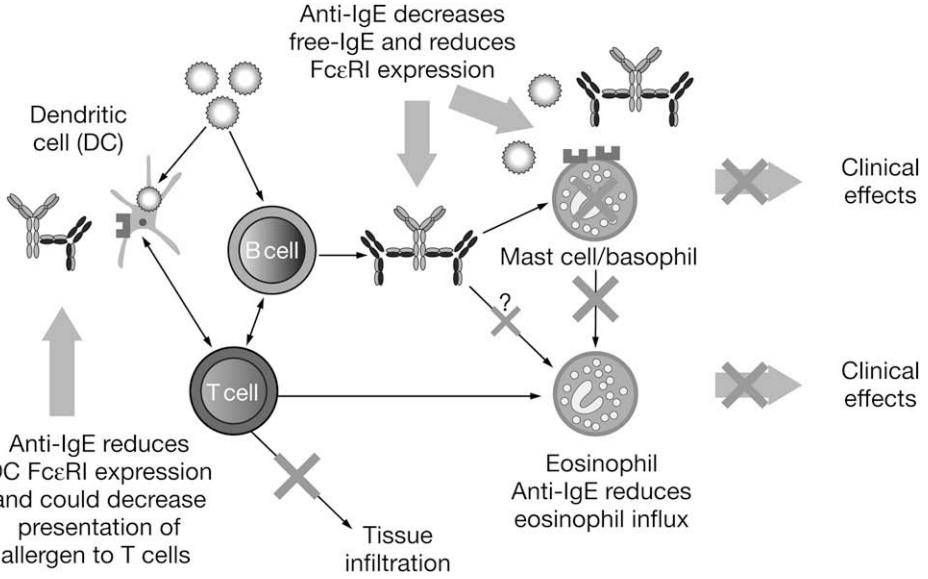


Figure 2 Proposed mechanisms of action of omalizumab.[5]

omalizumab is not able to cross-link FcεRI receptors and initiate the release of inflammatory mediators.

Clinical pharmacology

Omalizumab is absorbed slowly after subcutaneous administration, reaching peak serum concentrations after a mean of 7–8 days.[29] Clearance is slow (mean 2.4 ± 1.1 mL/kg/day) with a terminal half-life ($t_{1/2}$) of 26 days. No clinically important changes in the pharmacokinetics of omalizumab have been observed as a result of differences in age, sex or race.

Treatment with omalizumab has been shown to result in dose-dependent reductions in serum free IgE concentrations within 1 h of dosing. In phase III studies, the mean maximal decreases in serum free IgE were found to be greater than 96% of baseline levels.[34] Studies in patients with allergic asthma or rhinitis showed that clinical benefits with omalizumab are observed when serum free IgE levels are reduced to ≤50 ng/mL (20.8 IU/mL).[35–37] However, the ability of omalizumab to reduce free IgE levels to these levels is dependent on dose, the patient's weight and baseline serum total IgE level.[38] The target average free IgE level has been set at 25 ng/mL (10.4 IU/mL) to ensure that at least 95% of patients achieve a level below 50 ng/mL (20.8 IU/mL).[38] A dosing table has been developed to facilitate calculation of the omalizumab dose required to achieve the target reduction in free IgE, and is explained in more detail in the Dosing and administration section below.

Efficacy

Omalizumab is effective in patients with severe persistent allergic (IgE-mediated) asthma who are inadequately controlled despite optimized therapy (i.e. high-dose ICS plus LABA ± additional controller medication; GINA treatment step 4) and who have had multiple documented exacerbations in the previous year.[7,39] The INvestigatioN of Omalizumab in seVere Asthma TrEatment (INNOVATE) study evaluated the efficacy of omalizumab during 28 weeks of treatment in 419 patients with inadequately controlled, severe persistent allergic asthma despite optimized therapy.[39] Add-on omalizumab reduced the rate of clinically significant asthma exacerbations (asthma worsening requiring systemic corticosteroids) by 26% ($P = 0.042$) and severe exacerbations (peak expiratory flow [PEF] or forced expiratory volume in 1 s [FEV_1] <60% personal best and requiring systemic corticosteroids) by 50% ($P = 0.002$), compared with placebo.[39] In addition, the rate of emergency visits (hospital admissions, emergency room visits and unscheduled doctor's visits) was reduced by 44%, compared with placebo ($P = 0.038$). Based on these data, the number needed to treat (NNT) to prevent one clinically significant exacerbation per year is 2.7, and the NNTs to prevent one severe exacerbation and one emergency visit are 2.0 and 2.8 respectively.[40] Omalizumab also led to significant improvements in lung function (PEF, $P = 0.042$; FEV_1 (% of predicted), $P = 0.043$) and asthma symptoms ($P = 0.0398$) compared with placebo.

The findings of the INNOVATE study have been confirmed in a pooled analysis of seven efficacy trials involving a total of 4308 patients with predominantly severe persistent allergic asthma (93% had severe disease according to the GINA 2002 classification[7,41]). As in INNOVATE, omalizumab was administered as add-on therapy to current optimized asthma treatment in all seven studies. Add-on omalizumab was compared with placebo in five double-blind studies and with current asthma therapy alone in two open-label studies. Omalizumab-treated patients had an annualized asthma exacerbation rate of 0.91, compared with 1.47 in the control group (38.3% reduction; $P < 0.0001$). The pooled analysis also showed a significant reduction (47%) in the need for emergency medical care in those patients treated with omalizumab ($P < 0.0001$ compared with controls).

Safety, warnings and precautions

Omalizumab is well tolerated with a frequency and severity profile of adverse events (AEs) similar to that seen in patients receiving placebo or best available therapy.[42] AEs by system organ class and frequency for the total safety population treated with omalizumab in clinical trials are shown in Table 1. In controlled studies, a total of 2111 patients received omalizumab for 6 months, and 555 for at least 1 year.[42] The most frequently reported AEs with omalizumab were upper respiratory tract infection (16%), headache (16%), nasopharyngitis (14%) and sinusitis (10%). The majority of AEs were of mild-to-moderate severity and short duration. Injection-site reactions (of any severity) occurred in 45% of omalizumab-treated patients and 43% of placebo-treated patients, while severe injection-site

Table 1 Adverse reactions with omalizumab in clinical trials.[42]

Infections and infestations	
• Rare	Parasitic infection
Immune system disorders	
• Rare	Anaphylactic reaction, other serious allergic conditions
Nervous system disorders	
• Common	Headache
• Uncommon	Dizziness, somnolence, paraesthesia, syncope
Vascular disorders	
• Uncommon	Postural hypotension, flushing
Respiratory, thoracic and mediastinal disorders	
• Uncommon	Pharyngitis, coughing, allergic bronchospasm
Gastrointestinal disorders	
• Uncommon	Nausea, diarrhoea, dyspeptic signs and symptoms
Skin and subcutaneous tissue disorders	
• Uncommon	Urticaria, rash, pruritus, photosensitivity
General disorders and administration site conditions	
• Common	Injection-site reactions such as pain, erythema, pruritus, swelling
• Uncommon	Weight increase, fatigue, swelling arms, influenza-like illness

Frequencies are defined as: common (>1/100; <1/10), uncommon (>1/1,000; < 1/100) and rare (<1/1,000).

reactions occurred in 12% and 9% of omalizumab- and placebo-treated patients, respectively. Discontinuations due to AEs were uncommon (omalizumab 2%, control 1%) and the incidence of suspected drug-related AEs in placebo-controlled allergic asthma studies was similar in the omalizumab and placebo groups (9.2% vs 7.6%, respectively). Serious AEs were similar in omalizumab and control populations (omalizumab 4.2%, control 3.6%).

Allergic reactions

In clinical trials, anaphylaxis was reported in three out of 3507 (0.1%) patients: occurring with the first dose of omalizumab in two patients and with the fourth dose in one patient.[34] The time to onset of anaphylaxis was 90 min after administration in two patients and 2 h after administration in one patient. Based on post-marketing reports submitted to the Food and Drug Administration's Adverse Event Reporting System database and the manufacturers of omalizumab and cases published in the literature, 124 cases of anaphylaxis were identified in an estimated population of 57,300 patients who had received omalizumab in the United States between June 2003 and December 2006 (reporting rate 0.2%).[43] Approximately one-quarter of these patients had a prior history of anaphylaxis. Eighty-nine percent of patients displayed respiratory symptoms, 14% developed hypotension or syncope, and 19% required hospitalization. Several cases had a delayed onset, with symptoms occurring up to, and even beyond 24 h post-administration (Fig. 3). Anaphylactic events were reported after the second, third or more than third dose of omalizumab. The majority of patients responded to epinephrine, but several patients required multiple doses of epinephrine, bronchodilators and H_1-antihistamines. Anaphylaxis recurred in 78% of patients (18 out of 23) who were re-challenged with omalizumab. While it is possible to speculate on the mechanism (or mechanisms) of anaphylaxis with omalizumab based on evidence from published case studies, further studies are still needed. One report[44] suggested that reactions may be related to the excipient polysorbate rather than the omalizumab molecule itself,[45]

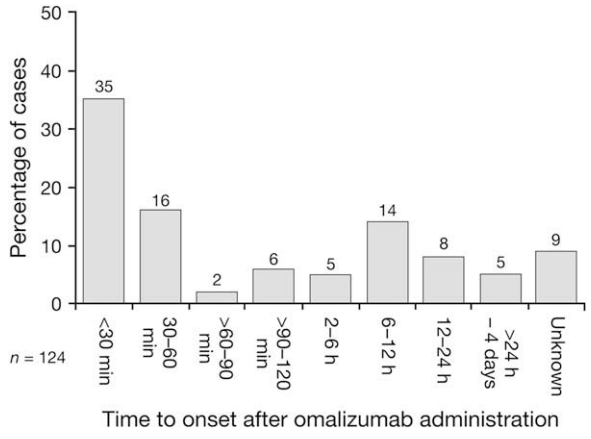


Figure 3 Time to onset of anaphylaxis cases ($n = 124$) in an estimated 57,300 patients who have received omalizumab in the United States.[43]

while reports of a lack of anti-omalizumab antibodies[44,46] and elevated circulating tryptase levels[46] may suggest mediator release from mast cells.

According to the EU label, it is recommended that medications should always be available for immediate use for the treatment of anaphylactic reactions following administration of omalizumab. In addition, patients should be warned of the potential for such reactions and, if allergic reactions occur, informed to seek prompt medical attention. Further recommendations for physicians regarding the patient observation period following omalizumab administration, including patient education on anaphylaxis, are provided in the report developed by the Omalizumab Joint Task Force (OJTF; The American Academy of Allergy, Asthma and Immunology and the American College of Allergy, Asthma and Immunology Executive Committees).[47,48] These include:

- Obtaining informed consent after discussing the risks, benefits and alternatives to omalizumab with the patient.
- Educating the patient regarding the signs, symptoms and treatment of anaphylaxis (Table 2).[49]
- Ensuring the patient is educated on the proper use of the epinephrine autoinjector and advised to carry this pre-administration and for 24 h post administration.
- Assessing the patient's current health status before each injection, including vital signs and some measure of lung function (e.g. PEF or FEV_1).
- The OJTF recommends that patients be kept under observation for 30 min after each injection. This time should be extended to 2 h for the first three injections.[47,50] However, this could be modified based on a physician's clinical judgment after discussing risks with the patient.

As with all recombinant DNA-derived humanized monoclonal antibodies, patients may in rare cases develop antibodies to omalizumab. In an analysis of all data collected from clinical trials up to November 2002, no cases of immunoreactivity to omalizumab have so far been found in those receiving omalizumab either subcutaneously or intravenously, however, one case has been detected in a patient who received omalizumab in an aerosolized form.[34] The development of antibodies may potentially lead to significant drug interference.

Serum sickness

When omalizumab binds to free IgE, small complexes of three or six molecules (trimers or hexamers) are formed.[51] Large immune complexes are a potential concern for the development of serum sickness, but the relatively small size of omalizumab-IgE trimeric and hexameric complexes and their inability to activate the complement cascade means that they are easily cleared from the body by the reticulo-endothelial system in the liver, bone marrow and spleen. While no AEs were reported as serum sickness in the omalizumab safety database, a search for event clusters that might be indicative of serum sickness revealed three omalizumab-treated patients and one control patient with serum sickness-like symptoms.[52] Additionally, one case

Table 2 Anaphylaxis education sheet.

Treatment of anaphylaxis in the physician's office[48]	Treatment of anaphylaxis in the community[49]
Immediate measures Assess airway breathing, circulation and orientation	Patient self-management after leaving the physician's office Information sheet on anaphylaxis with specific information on omalizumab Epinephrine autoinjector (EpiPen duopak or Twinject)
Inject epinephrine, 0.3 mg intramuscularly, in the vastus lateralis (lateral thigh) Activate emergency medical services (call 911 or local rescue squad)	Anaphylaxis Emergency Action Plan (downloadable from www.AAAAI.org)
Place patient in recumbent position and elevate the lower extremities, as tolerated Establish and maintain airway Administer oxygen Establish an intravenous line for venous access and fluid replacement; keep open with normal saline Consider administration of nebulized albuterol, 2.5—5 mg in 3 mL of saline; repeat as necessary Consider administration of ancillary medications, such as H_1 antihistamine or a systemic corticosteroid	Anaphylaxis wallet card (available from www.AAAAI.org at no charge to members and minimal charge for non-members) Medical identification jewellery tag (e.g. MedicAlert bracelet)

report of a severe serum sickness-like reaction to omalizumab has been published.[53]

Malignancies

Malignant neoplasms were reported in 20 of 5015 (0.5%) omalizumab-treated patients and five of 2854 (0.2%) control patients.[54] No cases of malignant neoplasia were considered drug-related when carefully assessed by a panel of independent oncologists, blinded to treatment assignment.[54] The overall observed incidence rate of malignancy in the omalizumab clinical trial programme was comparable to that reported in the general population: comparison with the National Institutes of Health (NIH) Surveillance, Epidemiology, and End Results (SEER) database showed that the standardized incidence ratio (95% confidence interval [CI]) of observed to expected number of malignant neoplasia events in the omalizumab group was 0.99 (0.55, 1.63) compared with 0.31 (0.04, 1.11) in the control group.[54] The diversity in the type of cancers observed, the relatively short duration of exposure and the clinical features of the individual cases make it most unlikely there is a causal relationship between omalizumab and malignancies.

Parasitic (helminth) infections

Although it is believed that IgE is involved in host defence mechanisms against parasitic infection, the overall helminth infection rate in the omalizumab clinical trial programme was found to be less than 1 in 1000 (Novartis, *data on file*). A slight increase in infection rate in patients receiving omalizumab was reported in one exploratory, randomized, double-blind, placebo-controlled trial in patients with allergic asthma or rhinitis and at high risk of parasitic infection.[55] Nevertheless, the time course, severity and response to treatment of infection were unaffected by omalizumab treatment. However, caution may be warranted in patients at high risk of helminth infection, in particular those travelling to areas where helminthic infections are endemic. If patients do not respond to recommended anti-helminth treatment, discontinuation of omalizumab should be considered.

Churg-Strauss syndrome and hypereosinophilic syndrome

Patients with severe asthma may rarely present with systemic hypereosinophilic syndrome or allergic eosinophilic granulomatous vasculitis (Churg-Strauss syndrome), both of which can usually be treated with systemic corticosteroids. As when treating with other anti-asthma therapies, physicians treating with omalizumab should be alert to the development of marked eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications and/or neuropathy.

Selection of patients for omalizumab treatment

Omalizumab is indicated in the EU as add-on therapy to improve asthma control in patients (12 years of age and above) with severe persistent allergic asthma who have the following characteristics:

- A positive skin test or *in vitro* reactivity (radioallergosorbent test [RAST]) to a perennial aeroallergen.
- Reduced lung function ($FEV_1 < 80\%$).
- Frequent daytime symptoms or night-time awakenings.
- Multiple documented severe asthma exacerbations.
- Receiving daily high-dose ICS plus a LABA (Fig. 4).

Omalizumab is included in the GINA 2007 guidelines at step 5, along with maintenance OCS, as an add-on therapy to high-dose ICS plus LABA. However, it is the only GINA step 5

add-on therapy with Category A evidence, i.e. a rich body of evidence from randomized controlled trials.[7] It should be noted that in the US, omalizumab is indicated for patients aged at least 12 years, who have moderate-to-severe persistent asthma with a positive skin test of *in vitro* reactivity to a perennial aeroallergen and are inadequately controlled using ICS. As described in the EU label, omalizumab treatment should only be considered for patients with convincing IgE-mediated asthma. Prescribing physicians should therefore ensure that patients with IgE below 76 IU/mL have an unequivocal RAST to a perennial allergen before starting therapy.

Predicting response

It is difficult to predict which patients will have the greatest benefit from treatment with omalizumab based on pre-treatment characteristics. The most accurate means of ensuring that omalizumab treatment is beneficial is to evaluate the response after a 16-week therapeutic trial (see Evaluating clinical response below).

Baseline IgE is the only variable found to have a broad predictive value based on extensive multi-variate analysis of data from the INNOVATE study. A lower baseline IgE was associated with a smaller treatment benefit (Table 3).[56] Subgroup analysis of the pooled population of patients enrolled in seven clinical trials (including INNOVATE) indicated that omalizumab reduced asthma exacerbation rates across four IgE quartiles: (1) 0—75 IU/mL; (2) 76—147 IU/mL; (3) 148—273 IU/mL; and (4) ≥274 IU/mL, but reached statistical significance in the three upper IgE quartiles only ($P < 0.001$).[56] Similarly, total emergency visit rates, proportions of responders with meaningful Asthma Quality of Life Questionnaire (AQLQ) improvements and FEV_1 net benefit favoured omalizumab-treated patients in the three upper IgE quartiles. However, for other outcomes there were benefits across all four quartiles, including severe exacerbation rates (statistically significant differences in quartiles 1, 3 and 4; $P < 0.05$) and the physician's overall assessment (statistically significant benefits in all IgE quartiles; $P < 0.05$).

No consistent predictive effect for omalizumab response has been observed for either total specific IgE load or for levels of IgEs specific for individual allergens (dust mite [*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*], cat dander, dog dander, cockroach, *Blatella germanica and Blatella orientalis*, *Aspergillus fumigatus*, and *Alternaria alternata*), either singly or in combination.[57] However, additional studies are required to further investigate and confirm these findings.

Dosing and administration

Dose determination

Dosing is determined by serum total IgE levels measured before initiation of omalizumab treatment and the patient's body weight, using a dosing table (Fig. 5). Once baseline serum IgE levels have been measured, it is not necessary to re-test IgE levels during treatment (total IgE levels rise and remain elevated during omalizumab treatment). However, dose adjustments will be necessary if there is a significant change in the patient's body weight. If this occurs, the pre-treatment serum IgE level and new body weight should be used to recalculate the dose.

More than double the number of under-dosed patients discontinued omalizumab therapy due to unsatisfactory

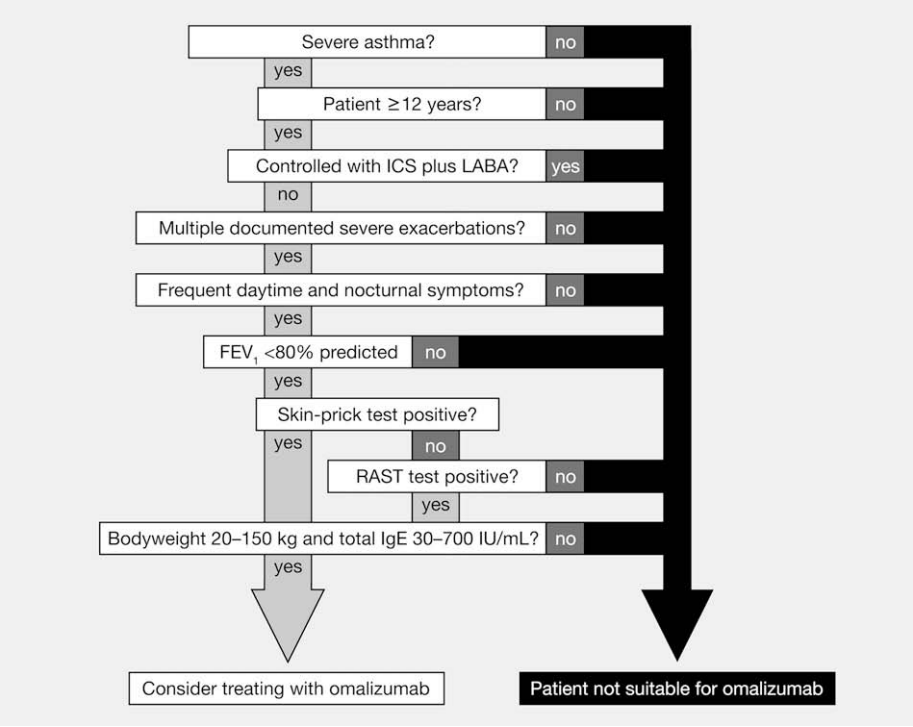


Figure 4 Selecting patients for omalizumab therapy. ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; FEV_1, forced expiratory volume in 1 s; RAST, radioallergosorbent test; IgE, immunoglobulin E.

Table 3 Efficacy outcomes in subgroups of patients divided in quartiles according to baseline IgE in the pooled population.[56]

Outcome measure	Baseline IgE subgroup							
	0–75 IU/mL		76–147 IU/mL		148–273 IU/mL		≥274 IU/mL	
	Omalizumab ($n = 602$)	Control ($n = 453$)	Omalizumab ($n = 659$)	Control ($n = 421$)	Omalizumab ($n = 634$)	Control ($n = 444$)	Omalizumab ($n = 616$)	Control ($n = 465$)
Annualized asthma exacerbation rate	1.28	1.48	0.85	1.47	0.80	1.47	0.76	1.43
Δ[a]		Δ −13.8%		Δ −41.9%		Δ −45.4%		Δ −46.5%
P-value		0.227		<0.001		<0.001		<0.001
Annualized severe exacerbation rate	0.09	0.22	0.07	0.11	0.07	0.20	0.05	0.17
Δ[a]		Δ −59.7%		Δ −38.0%		Δ −66.4%		Δ −68.8%
P-value		<0.05		0.218		<0.001		<0.001
Annualized total emergency visit rate	0.44	0.64	0.32	0.60	0.35	0.89	0.33	0.55
Δ[a]		Δ −31.0%		Δ −46.3%		Δ −60.9%		Δ −40.8%
P-value		0.141		<0.05		<0.01		<0.05
FEV_1 net benefit,[b] %	4.1	−0.5	11.7	3.4	7.9	0.5	22.3	2.9
P-value		0.289		0.057		0.099		<0.001
AQLQ improvement ≥0.5 points, %	58.7	54.2	67.5	54.0	68.7	50.0	68.9	52.5
P-value		0.298		<0.001		<0.001		<0.001
Physician's overall assessment,[c] %	49.3	40.2	59.3	42.9	66.6	36.1	67.1	36.2
P-value		<0.05		<0.001		<0.001		<0.001

[a] Δ Denotes the reduction in rate for omalizumab vs placebo.
[b] Patients with improvement in FEV_1 ≥200 mL minus those with worsening ≥200 mL, statistical testing was performed using proportions of patients with an improvement, a worsening, or no meaningful change.
[c] Complete control or marked improvement, *P*-value for the overall distribution of physician's overall assessment. Not all endpoints were assessed in each study.

therapeutic effect, compared with correctly dosed patients (i.e. 36.4% vs 15.0%) in a historic-prospective study of 147 patients in France who had received a nominative temporary use authorisation (ATU) for omalizumab between July 2003 and January 2006.[58] It is, therefore, essential that the correct dose of omalizumab is calculated and administered for each individual patient.

Preparation and administration

Omalizumab is provided as a sterile, white, preservative-free, lyophilized powder, which requires reconstituting with water. It should be administered as a subcutaneous injection every 2 or 4 weeks by a healthcare provider only. The solution is slightly viscous and the injections can take up to 30 s to administer. They are usually administered in the deltoid region of the arm or in the thigh. Each omalizumab vial is intended for single use only. Once reconstituted, omalizumab can be stored for up to 4 h at room temperature or up to 8 h in the refrigerator (2–8 °C). Reconstituted omalizumab vials also need to be protected from direct sunlight.

Dosing in patients with low or high IgE levels

The dosing schedule for omalizumab is based on the need to decrease free IgE levels. According to the EU label, the minimum baseline total IgE required for omalizumab treatment is 30 IU/mL. Although a clinical response to omalizumab was seen at all baseline IgE levels in the INNOVATE study, a response was less likely if the baseline IgE was below 76 IU/mL.[56] Patients with lower baseline total IgE may have, in general, lower levels of allergen-specific IgE and consequently might have a lower potential to respond to anti-IgE treatment.

At present, the dosing table for omalizumab is based on a maximum dose of 750 mg every 4 weeks, which precludes treatment of patients with IgE levels above 700 IU/mL. Studies are being conducted to investigate the treatment of patients with higher IgE levels (700–1500 IU/mL).

Evaluating clinical response

The physician's overall assessment (a composite measure that encompasses multiple aspects of response including patient interviews, review of medical notes, spirometry and diaries of symptoms, rescue medication use and peak expiratory flow) at 16 weeks has been determined to be the most meaningful measure for identifying responders and determining whether to continue treatment with omalizumab.[56] Only patients judged by the physician to have responded to therapy (i.e. shown a marked improvement in asthma control or complete asthma control) should

Panel A. Omalizumab doses (mg/dose) administered by subcutaneous injection every 4 weeks

Baseline IgE (IU/mL)	Body weight (kg)									
	>20–25	>25–30	>30–40	>40–50	>50–60	>60–70	>70–80	>80–90	>90–125	>125–150
≥30–100	75	75	75	150	150	150	150	150	300	300
>100–200	150	150	150	300	300	300	300	300		
>200–300	150	150	225	300	300					
>300–400	225	225	300							
>400–500	225	300	ADMINISTRATION EVERY 2 WEEKS SEE PANEL B							
>500–600	300	300								
>600–700	300									

Panel B. Omalizumab doses (mg/dose) administered by subcutaneous injection every 2 weeks

Baseline IgE (IU/mL)	Body weight (kg)									
	>20–25	>25–30	>30–40	>40–50	>50–60	>60–70	>70–80	>80–90	>90–125	>125–150
≥30–100	ADMINISTRATION EVERY 4 WEEKS SEE PANEL A									
>100–200									225	300
>200–300						225	225	225	300	375
>300–400				225	225	225	300	300		
>400–500			225	225	300	300	375	375		
>500–600			225	300	300	375				
>600–700		225	225	300	375	DO NOT ADMINISTER				

Figure 5 Omalizumab dosing table. IgE, immunoglobulin E.

continue therapy, as specified in the EU label (but not the US label) for omalizumab. Non-responders are categorized as those with discernible but limited control, no appreciable change or a worsening in control.[56] This also complies with current guideline recommendations for regular clinical review of patients with persistent asthma.[7]

In the EU, recommendation for using the physician's overall assessment to identify potential responders to omalizumab treatment is based on an analysis of the INNOVATE data and a pooled analysis that also included data from four additional randomized, double-blind, placebo-controlled clinical trials of ≥24 weeks' duration. This analysis identified 61% of patients as responders to omalizumab using the physician's overall assessment and provided accurate discrimination of exacerbation rates and other outcomes measures in responders vs non-responders (Table 4).[56] ''Responders'' were defined as those with marked improvement or complete control (graded in a five-level evaluation). In responders, annualized rates of clinically significant exacerbations were reduced by 60% (0.73 vs 1.84, $P < 0.001$ vs placebo), severe exacerbations by 76% (0.13 vs 0.54, $P < 0.001$ vs placebo) and total emergency visits by 76% (0.20 vs 0.85, $P < 0.0001$) (Novartis, data on file). These reductions illustrate the value of response evaluation when compared with the overall omalizumab-treated population in the INNOVATE study (reductions of 26%, 50% and 44%, respectively) at 28 weeks.[39] It should be noted, however, that using the asthma-related quality of life questionnaire (AQLQ) a high proportion of responders (% patients with ≥0.5 point increase in total AQLQ score[59,60]) was also identified, but this measure was not discriminative for severe exacerbation response. The Asthma Control Test[61] may also be a useful tool to assess response to omalizumab therapy; however, it was not available when the INNOVATE study was carried out. The test is being examined in ongoing studies.

The improved outcomes in responders in the 28-week, placebo-controlled INNOVATE study[39] have been confirmed by a *post-hoc* analysis[62] of the severe allergic asthma subpopulation from a 1-year, randomized, open-label study.[63] In the overall omalizumab-treated population of this study ($n = 115$) compared with those receiving best standard care only ($n = 49$), annual asthma exacerbation rate was reduced by 59% (1.26 vs 3.06; $P < 0.001$); asthma deterioration-related incident (ADRI) rate was reduced by 40% (5.61 vs 9.40; $P < 0.05$) and significant improvements were seen in lung function, asthma symptom scores and Mini-AQLQ overall score ($P < 0.05$). In the 70% of omalizumab-treated patients (71/102) who responded[f] to treatment, compared with best standard care, exacerbation rate was reduced by 64% (1.12 vs 3.07; $P < 0.001$), ADRI rate

[f] Defined in this study as those patients achieving ≥0.5-point improvement in Mini-AQLQ overall score at 27 weeks, as data relating to the physician's overall assessment was not collected in the original study.

Table 4 Annualized exacerbation rates, unscheduled healthcare utilization and other asthma control measures by physician's overall assessment responders and non-responders to omalizumab (INNOVATE study).[56]

	Responder	Non-responder
Clinically significant exacerbations		
Rate, mean (SD)	0.6 (1.31)	2.6 (6.39)
Severe exacerbations	0.2 (0.6)	1.4 (6.1)
Rate, mean (SD)	0.4	1.1
Hospitalizations[a]		
Patients hospitalized in treatment phase, %	2.5	9.1
Rate, mean (SD)	0.03 (0.22)	0.10 (0.35)
Emergency room visits[a]		
Rate, mean (SD)	0.02 (0.17)	0.17 (0.80)
Unscheduled physician visits[a]		
Rate, mean (SD)	0.11 (0.44)	0.49 (1.31)
Any unscheduled healthcare utilization		
Rate, mean (SD)	0.20 (0.61)	1.50 (6.14)
Asthma symptom score, mean (SD)[b]	−1.24 (1.82)	−0.47 (1.72)
Night awakenings due to asthma, per week mean (SD)[b]	−1.23 (2.22)	−0.28 (2.74)
Daily rescue medication use, puffs mean (SD)[b]	−2.32 (3.93)	−0.17 (3.79)
FEV_1 (mL), mean (SD)[b]	252 (521)	87 (445)
AQLQ improvement $\geq$0.5-point, % of patients	78.8	34.7

[a] Rates in the previous year were similar for responders and non-responders.
[b] Values are changes from baseline.

was reduced by 50% (4.71 vs 9.33; $P < 0.001$) and further improvements were seen in all other outcomes. The investigators proposed that this responder data, as assessed by a physician, reflects the actual benefit of omalizumab seen in clinical practice.

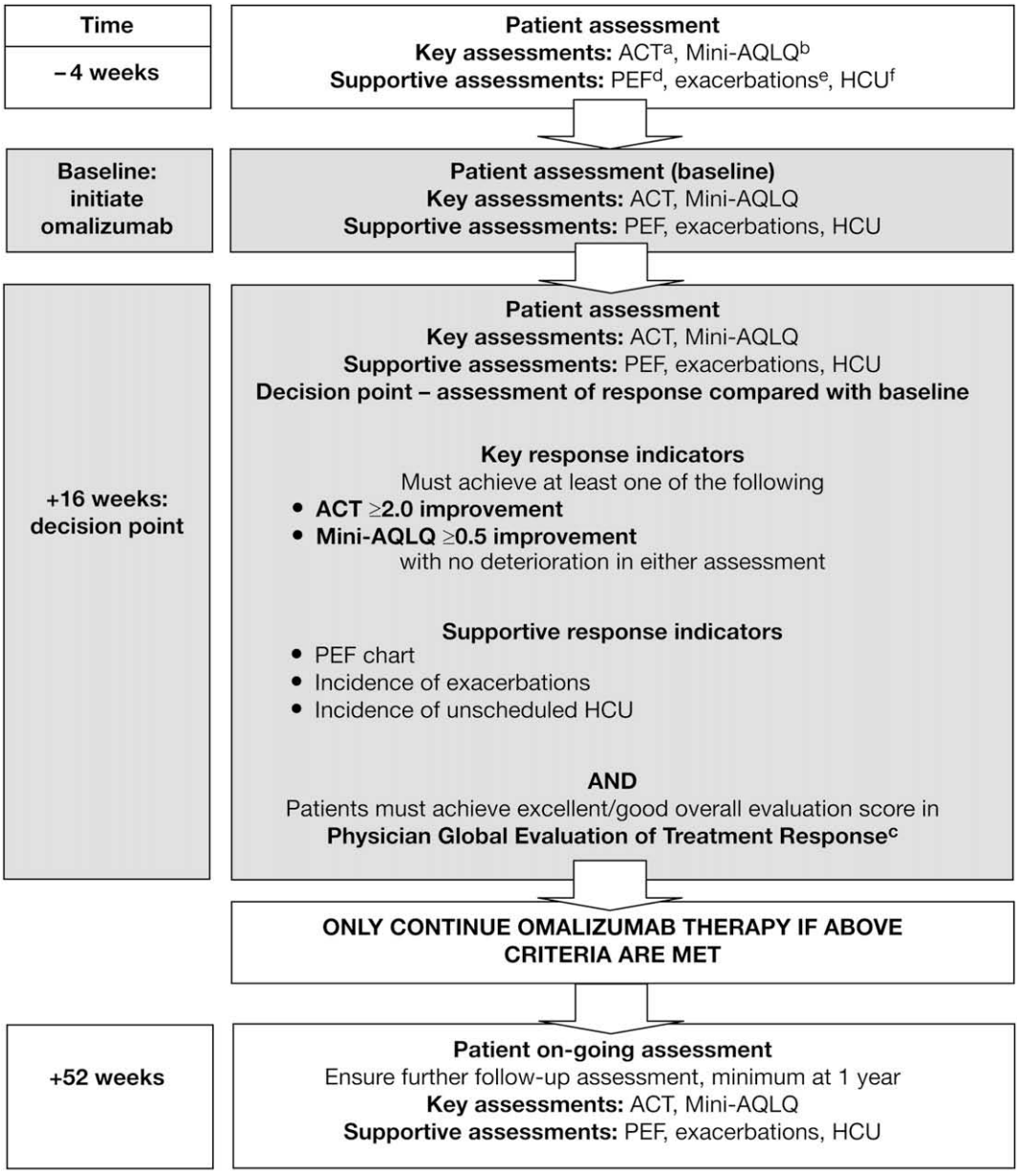
In the UK, an algorithm has been developed to assist physicians in determining patient response to omalizumab therapy following advice from the Scottish Medical Council (SMC) during reimbursement discussions. The SMC felt that the physician's overall assessment was too subjective, and physicians would benefit from a more robust guidance on assessing response. The resulting algorithm states that the final decision to continue with omalizumab therapy should be based on key assessment criteria (ACT, Mini-AQLQ and Physician Global Evaluation of Treatment Response), with supportive criteria (PEF, exacerbations and unscheduled healthcare utilization [HCU]) to aid physicians in the assessment of overall asthma control and lung function (Fig. 6).[64]

The recommended 16-week evaluation period is consistent with the mechanism of action of omalizumab and the progressive onset of action seen in clinical trials. A plateau of improvement in asthma symptoms and morning PEF has been identified at around 12—16 weeks[65] that most likely reflects the duration of IgE bound to effector cells and the down-regulation of FcεRI receptors on these cells. A pooled analysis of two multicentre, double-blind, randomized, placebo-controlled, phase III studies showed that the response to omalizumab was characterized by a progressive onset, with 38% of patients responding within 4 weeks of initiating treatment, compared with 64% at week 16.[66] In this analysis, responders were classified according to a composite measure (no exacerbations and one or more of the following: reduced symptoms, reduced rescue medication use, improved lung function, improved quality of life). In patients who were responders at 16 weeks, only 61% had responded at 4 weeks, 78% had responded by 8 weeks and 87% had responded by 12 weeks. Therefore, assessing response before 16 weeks may not identify 100% of patients who would respond to omalizumab. It is noteworthy that a quarter of the 28 patients who discontinued treatment due to an unsatisfactory effect in the historic-prospective French study had been treated for less than 16 weeks.[58]

The measure of evaluating patients' response to omalizumab using the physician's overall assessment will be further tested in the Evaluate Xolair for Asthma as Leading Treatment (EXALT) study of 400 patients with severe persistent allergic asthma treated with high-dose ICS plus a LABA, and to which omalizumab is added.[67] The study will assess how well a response at 16 weeks can also predict a response at 32 weeks. It will also examine whether the predictive power of the response measure can be further improved with the addition of further outcome measures, such as lung function, quality of life and asthma symptoms.

Duration of treatment and potential for dose reduction

Omalizumab is intended for long-term control of asthma and its efficacy and safety have been maintained in three long-term (i.e. 52-week) studies.[63,68,69] Additionally, withdrawal of treatment is not associated with AEs. In one study extension, after a 12-week washout period before restarting omalizumab, AEs were found to be similar between omalizumab and control, and similar to those observed in the core study. No adverse effect on the safety profile was noted.[70] During the clinical trials programme, after core treatment periods of 28—52 weeks, no evidence of withdrawal or rebound effects was seen during follow-up periods of 12—24 weeks (Novartis, *data on file*).



Key assessments

a. ACT: Asthma Control Test: 5-items, self-administered survey, assesses previous 4 weeks.
b. Mini-AQLQ (Asthma Quality of Life Questionnaire): 15 items, assesses previous 2 weeks.
c. Physician Global Evaluation Of Treatment Effectiveness: an overall clinical evaluation of improvement in asthma control at 16 weeks compared with baseline, based on all available information: patient interview, review of patient notes and diary (if used), and key and supportive response indicators; graded excellent, good, moderate, poor, or worsening; excellent/good evaluation indicates response to omalizumab treatment.

Supportive assessments

d. PEF: Peak Expiratory Flow, performed within 15 min of waking on Mon, Wed, Fri.
e. Exacerbations: worsening of asthma requiring additional oral corticosteroids. Patients should be exacerbation free for 4 weeks before baseline assessment.
f. HCU: Unscheduled Healthcare Utilization: hospitalization for asthma; A&E attendance; GP visit.

Figure 6 UK responder algorithm.[64]

It has been suggested that it may be possible to reduce omalizumab doses using a stepping down strategy, once asthma control has been improved. However, reducing omalizumab doses below those in the dosing table is not recommended as the resulting increase in free IgE leads to deterioration of asthma control.[71] A pharmacokinetic/pharmacodynamic model-based study used data from the INNOVATE study[39] and the 16-week follow-up period along with data from a single-dose bioequivalence study (Novartis, *data on file*) to plot free IgE, omalizumab and total IgE

concentrations against changes in measures of asthma control (total asthma symptom score, morning PEF and rescue medication use).[71] Model-derived omalizumab and free IgE concentrations correlated well with changes in clinical outcomes. Following treatment cessation, free IgE and omalizumab concentrations returned towards baseline and asthma symptoms re-emerged.[71] It is therefore recommended that omalizumab continues to be administered in accordance with the dosing table in those patients who respond and for as long as they continue to benefit from this treatment.

The ongoing EXCELS study will provide additional information on long-term efficacy and safety. EXCELS is a prospective, observational cohort study of non-omalizumab and omalizumab-treated patients from US clinical practices and is designed to characterize the long-term safety and effectiveness of omalizumab in up to 7500 patients during 5 years of follow up[10].

Comedications

In the EU, omalizumab is intended for use in conjunction with ICS and LABA. Nevertheless, in three studies omalizumab has been shown to reduce ICS requirements. In one randomized, double-blind, placebo-controlled study, median reductions in fluticasone dose were significantly greater with omalizumab than placebo (60% vs 50%; $P = 0.003$).[72] The trial involved a 16-week add-on phase and a 16-week fluticasone reduction phase. The large reduction in fluticasone dose in the placebo group was attributed to increased compliance with other controller medication in the clinical trial setting. Similar findings were reported in another study that also included a 12-week ICS reduction phase after 16 weeks of add-on omalizumab therapy; reductions in beclometasone dipropionate doses were significantly greater in patients receiving omalizumab (median 75%) than in those receiving placebo (50%; $P < 0.001$).[73] Omalizumab recipients were also more likely to discontinue ICS therapy (39.6%) than those receiving placebo (19.1%; $P < 0.001$). Again, a reduction in the corticosteroid dose was observed in the placebo group, presumably due to increased compliance. These findings are supported by those of a third study, which included an 8-week ICS reduction phase after 16 weeks of add-on omalizumab therapy.[74] Patients receiving omalizumab required lower beclometasone doses at the end of the corticosteroid-reduction phase (median 100 μg) than those receiving placebo (300 μg). Although these studies have shown that ICS dose reductions can be achieved in patients receiving add-on omalizumab therapy, it is important to remember that omalizumab is intended for use in conjunction with inhaled ICS and LABA in the EU (the US label does not require patients to be receiving a LABA). In addition, any decrease in ICS should be under the direct supervision of a physician, and needs to be performed gradually.

In the INNOVATE study, all patients were receiving high-dose ICS plus LABA.[39] However, approximately 60% of patients were also receiving additional controller medication (including maintenance OCS [22%], LTRAs [35%] and theophylline [27%]). Omalizumab has been shown to be effective in patients with severe persistent allergic asthma regardless of baseline OCS use. In a pooled analysis of seven controlled trials, omalizumab reduced exacerbation rates by 37% in patients who required OCS and by 39% in those who did not.[75] Omalizumab can, therefore, be considered for the treatment of inadequately controlled severe persistent allergic asthma, regardless of OCS use. A planned study of 450 patients in a naturalistic setting, which will include 100 OCS-dependent patients, is expected to provide further information on OCS use during treatment with omalizumab.

Omalizumab has been shown to significantly reduce the need for rescue OCS bursts irrespective of LTRA use. In a pooled analysis of three randomized trials, omalizumab reduced the need for OCS bursts by 51% in non-LTRA users (relative risk [omalizumab vs standard care]: 0.49; 95% CI 0.34—0.71; $P < 0.0001$) and by 53% in LTRA users (relative risk: 0.47; 95% CI 0.32—0.68; $P < 0.0001$).[76]

Effectiveness in clinical practice

Between June 2003 and April 2007, an estimated 63,000 patients with moderate-to-severe or severe persistent allergic asthma who are not adequately controlled on standard therapy have been treated with omalizumab worldwide, and more than 5000 patients received omalizumab in clinical trials. Several observational studies have provided data on the real-world effectiveness of omalizumab.

In the French historic-prospective study, the annual exacerbation rate decreased by 62% (6.0—2.3), emergency visits by 65% (3.1—1.1) and hospitalizations by 29% (1.7—1.2) for the 146 patients who had been prescribed omalizumab for severe allergic asthma between July 2003 and January 2006.[58] Compared with the year before treatment, the percentage of patients who did not have an asthma exacerbation during treatment more than doubled; those not having an emergency visit increased by 69%; and those not requiring hospitalization increased by 53%. Additionally, 25.6% of patients stopped using or lowered the dose of ICS, and 48.1% reduced or discontinued maintenance OCS. Overall, 26.5% of patients experienced at least one AE, and five patients experienced a severe AE. The most frequently reported AEs were headache ($n = 12$), asthenia ($n = 6$), local injection-site reaction ($n = 5$) and nausea ($n = 5$). Severe AEs were asthenia, irritability, headache, hypersensitivity convulsions, myalgia, arthralgia and periarthritis. Only two patients who experienced a severe AE discontinued treatment.

A German 6-month follow-up study conducted between 2005 and 2007 in 280 omalizumab-treated patients with severe persistent allergic IgE-mediated asthma reported marked reductions in daily symptoms (76%), nocturnal symptoms (84%), exacerbations (82%), unscheduled healthcare contacts (81%) and hospitalizations (78%).[77] Mean Mini-AQLQ score increased from 2.9 to 4.5, and treatment efficacy was rated as excellent or good by both physicians and patients (82% and 86%, respectively), thus confirming the clinically relevant effect of omalizumab. In this study, omalizumab-related AEs were reported in 7% of patients.

A small questionnaire-based observational study in 65 patients in the UK, who had continued with omalizumab therapy beyond 16 weeks found that out of 33 patients taking OCS at baseline, 18 (54.5%) had reduced their OCS and eight (24.2%) had stopped OCS altogether. The mean

relative reduction in OCS dose from baseline was 49% (22.6−11.6 mg, prednisolone equivalent).[78]

In the USA, omalizumab has been successfully adopted as a second-line therapy for inadequately controlled moderate or severe asthma in allergy and pulmonary practices.[79] Further data on the long-term (5 years) efficacy and safety of omalizumab in US clinical practices will be available upon completion (sometime after 2011) of the EXCELS study[10].

Comorbidity

Omalizumab has been shown to provide clinical benefits for comorbid conditions that frequently occur in patients with asthma. For example, omalizumab has been shown to be effective in the treatment of allergic rhinitis, which frequently coexists with asthma and is thought to share a common allergic inflammatory cause centred on IgE.[80] Omalizumab treatment results in substantial improvements in nasal symptoms, quality of life and rescue antihistamine use compared with placebo or specific immunotherapy in patients with allergic rhinitis.[37,81,82] A study has also shown that in patients with co-existing asthma and rhinitis, omalizumab treatment significantly reduces asthma, rhinitis and asthma/rhinitis composite symptom scores compared with placebo ($P \leq 0.02$).[83] Furthermore, analysis has shown that omalizumab-treated asthma ''responders'' (i.e. demonstrating a marked improvement in asthma control or complete asthma control according to the physician's overall assessment) were more likely to experience a rhinitis response than omalizumab-treated asthma non-responders: the odds ratio for a $\geq$1.0-point improvement in the Rhinitis Quality of Life Questionnaire (RQLQ) overall score[84] in asthma responders vs non-responders was 3.56 (95% CI 1.94−6.54) and for a $\geq$1.5-point improvement in the RQLQ overall score the odds ratio was 3.79 (95% CI 2.11−6.82).[85]

Although omalizumab is not indicated for the treatment of allergic rhinitis, it may provide additional benefits in patients with severe persistent allergic asthma and concomitant rhinitis, particularly in patients who achieve a marked improvement or complete asthma control with omalizumab.[85]

Discussion

Omalizumab has been successfully adopted into clinical practice, with more than 68,000 patients treated worldwide since June 2003. Observational studies have shown important benefits for many patients with inadequately controlled severe persistent allergic asthma who respond to omalizumab therapy. This supports the results from the comprehensive clinical trial programme, in which omalizumab significantly reduced asthma exacerbation and emergency visit rates, and significantly improved quality of life in patients with severe persistent allergic asthma. Consequently, omalizumab is indicated in the EU as add-on therapy to improve control of severe persistent allergic asthma that remains inadequately controlled despite treatment with high-dose ICS and a LABA. In 2007, the UK National Institute for Health and Clinical Excellence (NICE) approved public reimbursement of add-on omalizumab for the treatment of severe persistent allergic (IgE-mediated) asthma where, in addition to the label criteria, patients should have experienced two or more severe exacerbations requiring hospitalization within the previous year, or three or more severe exacerbations within the previous year, one requiring hospitalization, and two requiring treatment or monitoring in an accident and emergency unit.[86] The label in the US is different; omalizumab is indicated for moderate-to-severe asthma that is uncontrolled despite treatment with high-dose ICS. In some clinical trials, omalizumab has demonstrated efficacy in patients with rhinitis and patients with co-existing asthma and allergic rhinitis, although it is not indicated for this comorbidity.

Analyses of patients treated in clinical trials have shown that it is difficult to predict which patients, within the label population, will derive greatest benefit from omalizumab based on pre-treatment patient characteristics. In the EU, it is recommended that treatment is initiated in eligible patients and the response evaluated by the physician after 16 weeks of therapy. Treatment should be continued in patients who are judged by the physician to have achieved a marked improvement or complete asthma control. Using this method of assessment, the analysis by Bousquet et al. indicates that approximately 60% of patients could be expected to be identified as responders to omalizumab.[56]

It is recommended that omalizumab be dosed according to the patient's body weight and pre-treatment total IgE levels (30−700 IU/mL) using the dosing table (Fig. 5). Omalizumab is administered by subcutaneous injection every 2 or 4 weeks and should be continued in those patients who respond for as long as they continue to benefit from this treatment. Reducing the omalizumab dose can cause deterioration of asthma control and is not recommended. A small study has found that 1 year after cessation of omalizumab following 6 years of treatment, patients' asthma symptoms were similar to when they were receiving omalizumab,[87] indicating that omalizumab has the potential to actually modify the disease. Basophil reactivity was also significantly reduced compared with controls ($P < 0.001$). Although omalizumab therapy may potentially have some disease-modifying properties, further investigation is needed. A prospective study is currently underway that aims to assess the effect of 78 weeks of omalizumab therapy on airway sub-epithelial eosinophils and other markers of airway inflammation and remodelling, through the collection of bronchial biopsies and induced sputum samples.

The reason why not all patients respond to omalizumab therapy is unclear. In clinical practice, correct diagnosis of allergic (IgE-mediated) asthma is essential, and potential comorbidities should be considered. One study reported that 12% of patients with difficult-to-treat asthma who remained symptomatic despite treatment with >1000 μg beclometasone dipropionate (or equivalent) and a LABA did not have asthma, and a further 7% had additional diagnoses such as bronchiectasis or hypereosinophilia.[88] Analysis of INNOVATE data has shown that IgE is equally well suppressed in omalizumab responders and non-responders.[71] Therefore, if patient selection and omalizumab

administration are correct, it may be that IgE is not driving asthma in some of these cases.

Overall, by careful patient selection and dosing, and monitoring of patients following administration, omalizumab can be effectively and safely administered, and control of a high proportion of persistent severe allergic asthma cases can be successfully achieved.

Acknowledgements

The authors were assisted in the preparation of this text by professional medical writers, Dr. Dominic Hague (contracted) and Thomas McMurray (ACUMED®) and editorial assistance was provided by Helen Venables (ACUMED®); this support was funded by Novartis Pharma AG.

Conflict of interest

SH has undertaken consultancy and lecturing work in relation to omalizumab and has participated in several of the clinical trials referred to in this review.

RB has received reimbursement for attending scientific conferences, and/or fees for speaking and/or consulting from Nycomed, Asche Chiesi, AstraZeneca, Bayer, Boehringer Ingelheim, GlaxoSmithKline, Janssen-Cilag, Merck, Merck Sharp & Dohme, Novartis, and Pfizer. The Pulmonary Department at Mainz University Hospital received financial compensation for services performed during participation in single- and multi-center clinical phase I—IV trials organized by various pharmaceutical companies.

JB has received honorarium for consultations and lectures from Novartis.

NS, ZP and PJ are employees of Novartis Pharmaceuticals.

References

1. Walker S, Monteil M, Phelan K, Lasserson TJ, Walters EH. Anti-IgE for chronic asthma in adults and children. Issue 2. Art. No.: CD003559. *Cochrane Database Syst Rev* 2006. doi: 10.1002/14651858.CD003559.pub3.
2. Prenner BM. Asthma 2008: targeting immunoglobulin E to achieve disease control. *J Asthma* 2008;**45**:429—36.
3. Price D. The use of omalizumab in asthma. *Prim Care Respir J* 2008;**17**:62—72.
4. Corren J, Casale TB, Lanier B, Buhl R, Holgate S, Jimenez P. Safety and tolerability of omalizumab. Clin Exp Allergy, in press. doi: 10.1111/j.1365-2222.2009.03214.x.
5. Holgate S, Casale T, Wenzel S, Bousquet J, Deniz Y, Reisner C. The anti-inflammatory effects of omalizumab confirm the central role of IgE in allergic inflammation. *J Allergy Clin Immunol* 2005;**115**:459—65.
6. Sullivan SD, Turk F. An evaluation of the cost-effectiveness of omalizumab for the treatment of severe allergic asthma. *Allergy* 2008;**63**:670—84.
7. Global Initiative for Asthma. Global strategy for asthma management and prevention. Issued January 1995 (NIH Publication No. 02-3659); updated 2002, 2003, 2004, 2005, 2006, 2007. Available at: www.ginasthma.org.
8. American Thoracic Society. Proceedings of the ATS workshop on refractory asthma: current understanding, recommendations, and unanswered questions. *Am J Respir Crit Care Med* 2000;**162**:2341—51.
9. Bateman ED, Boushey HA, Bousquet J, et al. Can guideline-defined asthma control be achieved? The gaining optimal asthma control study. *Am J Respir Crit Care Med* 2004;**170**:836—44.
10. Fish J, Miller K, Bradley S, Szefler S. Characteristics of omalizumab-treated patients in the EXCELS study. *Am J Respir Crit Care Med* 2008;**177**(Abstracts issue):A613.
11. Dolan CM, Fraher KE, Bleecker ER, et al. Design and baseline characteristics of the epidemiology and natural history of asthma: outcomes and treatment regimens (TENOR) study: a large cohort of patients with severe or difficult-to-treat asthma. *Ann Allergy Asthma Immunol* 2004;**92**:32—9.
12. Guite HF, Dundas R, Burney PGJ. Risk factors for death from asthma, chronic obstructive pulmonary disease, and cardiovascular disease after a hospital admission for asthma. *Thorax* 1999;**54**:301—7.
13. Hartert TV, Speroff T, Togias A, et al. Risk factors for recurrent asthma hospital visits and death among a population of indigent older adults with asthma. *Ann Allergy Asthma Immunol* 2002;**89**:467—73.
14. Tough SC, Hessel PA, Ruff M, Green FH, Mitchell I, Butt JC. Features that distinguish those who die from asthma from community controls with asthma. *J Asthma* 1998;**35**:657—65.
15. Juniper EF, Wisniewski ME, Cox FM, Emmett AH, Nielsen KE, O'Byrne PM. Relationship between quality of life and clinical status in asthma: a factor analysis. *Eur Respir J* 2004;**23**:287—91.
16. Turk F, Piercy J, Benford M. The human impact of severe persistent allergic asthma; results of a multinational study. *Value Health* 2005;**8**:A32.
17. Godard P, Chanez P, Siraudin L, Nicoloyannis N, Duru G. Costs of asthma are correlated with severity: a 1-yr prospective study. *Eur Respir J* 2002;**19**:61—7.
18. Antonicelli L, Bucca C, Neri M, et al. Asthma severity and medical resource utilisation. *Eur Respir J* 2004;**23**:723—9.
19. Turk F, Kay S, Higgins V. The economic and human impact of poor control in patients with severe persistent allergic asthma: results from a multinational study. *Thorax* 2005;**60**(Suppl. II):P21.
20. Serra-Battles J, Plaza V, Morejón E, Comella A, Brugués J. Costs of asthma according to the degree of severity. *Eur Respir J* 1998;**12**:1322—6.
21. ENFUMOSA. The ENFUMOSA cross-sectional European multicentre study of the clinical phenotype of chronic severe asthma. *Eur Respir J* 2003;**22**:470—7.
22. Hammad H, Lambrecht BN. Dendritic cells and epithelial cells: linking innate and adaptive immunity in asthma. *Nat Rev Immunol* 2008;**8**:193—204.
23. Prussin C, Metcalfe DD. IgE, mast cells, basophils, and eosinophils. *J Allergy Clin Immunol* 2003;**111**:S486—94.
24. Novak N, Bieber T. Allergic and nonallergic forms of atopic diseases. *J Allergy Clin Immunol* 2003;**112**:252—62.
25. Jaffar Z, Roberts K, Pandit A, Linsley P, Djukanović R, Holgate S. B7 costimulation is required for IL-5 and IL-13 secretion by bronchial biopsy tissue of atopic asthmatic subjects in response to allergen stimulation. *Am J Respir Cell Mol Biol* 1999;**20**:153—62.
26. Djukanović R, Wilson SJ, Kraft M, et al. Effects of treatment with anti-immunoglobulin E antibody omalizumab on airway inflammation in allergic asthma. *Am J Respir Crit Care Med* 2004;**170**:583—93.
27. MacGlashan Jr DW, Bochner BS, Adelman DC, et al. Down-regulation of Fc(ε)RI expression on human basophils during in vivo treatment of atopic patients with anti-IgE antibody. *J Immunol* 1997;**158**:1438—45.
28. Gould HJ, Sutton BJ. IgE in allergy and asthma today. *Nat Rev Immunol* 2008;**8**:205—17.
29. Lin H, Boesel KM, Griffith DT, et al. Omalizumab rapidly decreases nasal allergic response and FcεRI on basophils. *J Allergy Clin Immunol* 2004;**113**:297—302.

30. Humbles AA, Lloyd CM, McMillan SJ, et al. A critical role for eosinophils in allergic airways remodeling. *Science* 2004;**305**: 1776–9.
31. Lee JJ, Dimina D, Macias MP, et al. Defining a link with asthma in mice congenitally deficient in eosinophils. *Science* 2004; **305**:1773–6.
32. Presta L, Shields R, O'Connell L, et al. The binding site on human immunoglobulin E for its high affinity receptor. *J Biol Chem* 1994;**269**:26368–73.
33. Shields RL, Whether WR, Zioncheck K, et al. Inhibition of allergic reactions with antibodies to IgE. *Int Arch Allergy Immunol* 1995;**107**:308–12.
34. Genentech Inc. Omalizumab (Xolair®) full prescribing information, July 2007. Available at: http://www.gene.com/gene/products/information/immunological/xolair/insert.jsp. Accessed 02 June 2008.
35. Boulet LP, Chapman KR, Côté J, et al. Inhibitory effects of an anti-IgE antibody E25 on allergen-induced early asthmatic response. *Am J Respir Crit Care Med* 1997;**155**:1835–40.
36. Casale TB, Bernstein IL, Busse WW, et al. Use of an anti-IgE humanized monoclonal antibody in ragweed-induced allergic rhinitis. *J Allergy Clin Immunol* 1997;**100**:110–21.
37. Ädelroth E, Rak S, Haahtela T, et al. Recombinant humanized mAb-E25, an anti-IgE mAb, in birch pollen-induced seasonal allergic rhinitis. *J Allergy Clin Immunol* 2000;**106**:253–9.
38. Hochhaus G, Brookman L, Fox H, et al. Pharmacodynamics of omalizumab: implications for optimised dosing strategies and clinical efficacy in the treatment of allergic asthma. *Curr Med Res Opin* 2003;**19**:491–8.
39. Humbert M, Beasley R, Ayres J, et al. Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. *Allergy* 2005;**60**:309–16.
40. Humbert M, Ayre G, Fox H, Blogg M. Number needed to treat to prevent one medically significant event per year with add-on omalizumab: INNOVATE. *EAACI Abstract Book* 2006;**41**:125.
41. Bousquet J, Cabrera P, Berkman N, et al. The effect of treatment with omalizumab, an anti-IgE antibody, on asthma exacerbations and emergency medical visits in patients with severe persistent asthma. *Allergy* 2005;**60**:302–8.
42. Corren J, Casale T, Lanier BQ. Omalizumab is well tolerated in adolescent/adult patients (>12 years) with moderate-to-severe asthma. *J Allergy Clin Immunol* 2005;**115**:S75.
43. Limb S, Starke P, Lee C, Chowdhury B. Delayed onset and protracted progression of anaphylaxis after omalizumab administration in patients with asthma. *J Allergy Clin Immunol* 2007;**120**:1378–81.
44. Price KS, Hamilton RG. Anaphylactoid reactions in two patients after omalizumab administration after successful long-term therapy. *Allergy Asthma Proc* 2007;**28**:313–9.
45. Lieberman P. The unusual suspects: a surprise regarding reactions to omalizumab. *Allergy Asthma Proc* 2007;**28**:259–61.
46. Chipps B. Systemic reaction to omalizumab. *Ann Allergy Asthma Immunol* 2006;**97**:267.
47. Cox L, Platts-Mills TA, Finegold I, Schwartz LB, Simons FE, Wallace DV. American Academy of Allergy, Asthma and Immunology/American College of Allergy, Asthma and Immunology Joint Task Force Report on omalizumab-associated anaphylaxis. *J Allergy Clin Immunol* 2007;**120**:1373–7.
48. Joint Task Force on Practice Parameters; American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. The diagnosis and management of anaphylaxis: an updated practice parameter. *J Allergy Clin Immunol* 2005; **115**(Suppl.):S483–523.
49. Simons FE. Anaphylaxis, killer allergy: long-term management in the community. *J Allergy Clin Immunol* 2006;**117**:367–77.
50. National Heart Lung and Blood Institute. Expert Panel Report 3 (EPR3): Guidelines for the diagnosis and management of asthma 2007. Available at: http://www.nhlbi.nih.gov/guidelines/asthma/index.htm. Accessed 02 June 2008.
51. Liu J, Lester P, Builder S, Shire J. Characterization of complex formation by humanized anti-IgE monoclonal antibody and monoclonal human IgE. *Biochemistry* 1995;**34**:10474–82.
52. US Food and Drug Administration. *Center for Biologics Evaluation and Research. BLA STN 103976/0, briefing document on safety*. Rockville, MD: Genentech Inc.; 2003. Department of Health and Human Services.
53. Pilette C, Coppens N, Houssiau F, Rodenstein D. Severe serum sickness-like syndrome after omalizumab therapy for asthma. *J Allergy Clin Immunol* 2007;**120**:972–3.
54. Fernández C, Busse W, Reisner C, Gupta N. Clinical data do not suggest a causal relationship between omalizumab therapy and cancer. *Proc Am Thorac Soc* 2005;**2**:A359.
55. Cruz AA, Lima F, Sarinho E, et al. Safety of anti-immunoglobulin E therapy with omalizumab in allergic patients at risk of geohelminth infection. *Clin Exp Allergy* 2007;**37**:197–207.
56. Bousquet J, Rabe K, Humbert M, et al. Predicting and evaluating response to omalizumab in patients with severe allergic asthma. *Respir Med* 2007;**101**:1483–92.
57. Martin C, Freeman P, Blogg M. Pre-treatment specific IgE levels are not useful in predicting a response to omalizumab therapy. *J Allergy Clin Immunol* 2008;**121**:S171.
58. Molimard M, de Blay F, Didier A, Le Gros V. Effectiveness of omalizumab (Xolair) in the first patients treated in real-life practice in France. *Respir Med* 2008;**102**:71–6.
59. Juniper EF, Guyatt GH, Epstein RS, Ferrie PJ, Jaeschke R, Hiller TK. Evaluation of impairment of health related quality of life in asthma: development of a questionnaire for use in clinical trials. *Thorax* 1992;**47**:76–83.
60. Juniper EF, Guyatt GH, Willan A, Griffith LE. Determining a minimal important change in the disease specific quality of life questionnaire. *J Clin Epidemiol* 1994;**47**:81–7.
61. Schatz M, Sorkness CA, Li JT, et al. Asthma Control Test: Reliability, validity, and responsiveness in patients not previously followed by asthma specialists. *J Allergy Clin Immunol* 2006;**117**:549–56.
62. Niven R, Chung KF, Panahloo Z, et al. Effectiveness of omalizumab in patients with inadequately controlled severe persistent allergic asthma: an open-label study. *Respir Med* 2008; **102**(10):1371–8.
63. Ayres JG, Higgins B, Chilvers ER, Ayre G, Blogg M, Fox H. Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with poorly controlled (moderate-to-severe) allergic asthma. *Allergy* 2004;**59**:701–8.
64. Thomson N, Niven R, Heaney L, Greening A. Development of an algorithm for the assessment of response to treatment with omalizumab. *Thorax* 2007;**62**(Suppl. 3): A99, P94.
65. Holgate ST. How to evaluate a patient's response to anti-IgE. *Eur Respir Rev* 2007;**16**:78–84.
66. Bousquet J, Wenzel S, Holgate S, Lumry W, Freeman P, Fox H. Predicting response to omalizumab, an anti-IgE antibody, in patients with allergic asthma. *Chest* 2004;**125**:1378–86.
67. Ayre G, Anthonissen C, Martin C, Turk F, Thomas K. Assessment of a responder identification treatment algorithm for omalizumab in a naturalistic setting. *Eur Respir J* 2007;**30**(Suppl. 51): 623s, P3654.
68. Buhl R, Solèr M, Matz J, et al. Omalizumab provides long-term control in patients with moderate-to-severe allergic asthma. *Eur Respir J* 2002;**20**:73–8.
69. Lanier BQ, Corren J, Lumry W, Liu J, Fowler-Taylor A, Gupta N. Omalizumab is effective in the long-term control of severe allergic asthma. *Ann Allergy Asthma Immunol* 2003;**91**:154–9.
70. Bousquet J, Chung F, Tunon-de-Lara JM, et al. Retreatment with omalizumab, an anti-IgE monoclonal antibody, is well

tolerated in patients with severe allergic asthma. *Allergy* 2003; **58**(Suppl.). 2, A4.
71. Slavin R, Ferioli C, Tannenbaum S, et al. Asthma symptom re-emergence after omalizumab withdrawal correlates well with increasing immunoglobulin-E and decreasing pharmacokinetic concentrations. J Allergy Clin Immunol 2009;**123**(1): 107—113, e3.
72. Holgate ST, Chuchalin AG, Hébert J, et al. Efficacy and safety of a recombinant anti-immunoglobulin E antibody (omalizumab) in severe allergic asthma. *Clin Exp Allergy* 2004;**34**:632—8.
73. Busse W, Corren J, Lanier BQ, et al. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. *J Allergy Clin Immunol* 2001; **108**:184—90.
74. Solèr M, Matz J, Townley R, et al. The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics. *Eur Respir J* 2001;**18**:254—61.
75. Wenzel S, Hébert J, Buhl R, et al. Add-on omalizumab therapy significantly reduces asthma exacerbations in patients with severe persistent asthma requiring maintenance oral corticosteroids: a pooled analysis. *Proc Am Thorac Soc* 2005;**2**:A358.
76. Zeldin R, Massanari M, Maykut R, et al. Omalizumab reduced the need for steroid bursts in asthmatics concomitantly using leukotriene receptor antagonists (LTRAs). *J Allergy Clin Immunol* 2006;**117**:S280.
77. Korn S, Thielen A, Seyfried S, Kornmann O, Buhl R. Omalizumab in patients with uncontrolled, severe persistent allergic (IgE-mediated) asthma in a real-life setting in Germany. *Am J Respir Crit Care Med* 2008;**177**(Abstracts issue):A612.
78. Niven R. A UK survey of oral corticosteroid use in patients treated with omalizumab. *Thorax* 2007;**62**(Suppl. 3): A98, P91.
79. Marcus P. Incorporating anti-IgE (omalizumab) therapy into pulmonary medicine practice: practice management implications. *Chest* 2006;**129**:466—74.
80. Bousquet J, Vignola AM, Demoly P. Links between rhinitis and asthma. *Allergy* 2003;**58**:691—706.
81. Price D, Zhang Q, Kocevar S, et al. Effect of concomitant diagnosis of allergic rhinitis on asthma-related health care use in adults. *Clin Exp Allergy* 2005;**35**:282—7.
82. Casale TB, Condemi J, LaForce C, et al. Effect of omalizumab on symptoms of allergic rhinitis. A randomized controlled trial. *JAMA* 2001;**286**:2956—67.
83. Vignola AM, Humbert M, Bousquet J, et al. Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with concomitant allergic asthma and persistent allergic rhinitis: SOLAR. *Allergy* 2004;**59**:709—17.
84. Juniper EF, Guyatt GH. Development and testing of a new measure of health status for clinical trials in rhinoconjunctivitis. *Clin Exp Allergy* 1991;**21**:77—83.
85. Humbert M, Boulet LP, Niven RM, Panahloo Z, Blogg M, Ayre G. Omalizumab therapy: patients who achieve greatest benefit for their asthma experience greatest benefit for rhinitis. Allergy 2009;**64**(1):81—84.
86. National Institute For Health And Clinical Excellence. Final appraisal determination omalizumab for severe persistent allergic asthma. 2007. Available from: http://guidance.nice.org.uk/download.aspx?o = 450310. Accessed 18 September 2007.
87. Nopp A, Johansson SG, Ankerst J, Palmqvist M, Oman H. CD-sens and clinical changes during withdrawal of Xolair after 6 years of treatment. *Allergy* 2007;**62**:1175—81.
88. Robinson DS, Campbell DA, Durham SR, et al. Systematic assessment of difficult-to-treat asthma. *Eur Respir J* 2003;**22**: 478—83.